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(54) Title: NEW BEADS FOR CONTROLLED RELEASE AND A PHARMACEUTICAL PREPARATION CONTAINING THE SAME

(57) Abstract

Controlled release beads containing a core around which is a drug-containing layer e.g. a layer containing furosemid and a process for their preparation and their use in a pharmaceutical preparation. The controlled release beads have excellent mechanical and release characteristics.

NEW BEADS FOR CONTROLLED RELEASE AND A PHARMACEUTICAL PREPARATION CONTAINING THE SAME.

Field of the invention

The present invention relates to controlled release beads and a novel pharmaceutical preparation containing a core around which is a drug-containing layer e.g. a layer containing an active substance, i.e. a practically insoluable active substance, preferably furosemid to the use of said preparation and to a process for preparing the same.

Background of the invention

The present invention provides a novel a pharmaceutical multiple unit dose preparation with very favourable characteristics which may withstand mechanical stress, i.e. during compaction. These favourable mechanical characteristics are advantageous when dealing with multiple unit dose systems comprising modified or controlled release properties.

A common problem with multiple unit dose systems designated to have modified or controlled release properties is their sensitivity to mechanical stress, e.g. compaction stress, giving rise to rupturing and cracking of the release controlling membrane (Bechard and Leroux 1992) or fragmentation of the core (Magnatiand Celik 1994).

Multiple unit dosage systems may be filled into capsules or sachets, thus requiring sufficient mechanical properties to withstand processing. It may even be advantageous to compact multiple units into tablets, subjecting the systems to significant mechanical stress.

According to the present invention the problem of mechanical suitability mentioned above has been overcome by using inert and non-soluble cores of glass or sand

particles or soluble cores such as sugar spheres capable of withstanding mechanical stress, in combination with a plasticizing layer of a hydrophilic polymer containing the active substance, optionally with additional layers of the polymer not containing the active substance, layered between the core and the release controlling membrane.

Prior art

In abstract PDD 7397 from AAPs congress, USA, Pharmaceutical Research (supplement), 1993, it is described that the coating of pellets provides a physical protection of the pellet core which must remain intact and have suitable mechanical properties in order to be resistant to fragmentation during compaction of the tablet. Fragmentation was, however, found to be between 18 and 42% for ethylcellulose pellets.

In Drug Development and Industrial Pharmacy, 18(8), 1927-1944 (1992), films manufactured from an ethyl cellulose pseudolatex dispersion plasticized with 24% DBS, suitable for the controlled release of chlorpheniramine maleate from small pellets with a size of 250-840 mm, are described. These films do not, however, have the appropriate mechanical properties to withstand compaction forces without rupturing, and the controlled release properties of the compacted pellets are thus lost during the process.

In "Compaction studies on pellets", L. Maganti and M. Celik, International Journal of Pharmaceutics, 95 (1993) 29-42, compaction characteristics of pellets, i.e. cores made from microcrystalline cellulose, dicalciumphosphate, lactose and propranolol HCl, are described, and it is concluded that the pellets exhibit elastic deformation and brittle fragmentation, resulting in compacts of lower tensile strength.

In "Compaction studies on pellets", L. Maganti and M. Celik, International Journal of Pharmaceutics, 103 (1994) 55-67, it is described that the addition of a coating material alters the deformation characteristics of uncoated pellets. Further, it is shown that coated pellets lost their sustained release characteristics after compaction.

US patent 4,713,248 describes a controlled release multiple unit formulation containing an active substance coated with a water based film comprising a homogeneous combination of water-dispersable film forming agent and a polymeric substance which impart compressability to the coating.

EP 361 874 describes a process for the preparation of a core by spraying core granules with a dispersion of a low substituted hydroxypropylcellulose, and if necessary simultaneously applying a dusting powder. The dispersion or the dusting powder can be incorporated with an active ingredient. The granules obtained exhibit increased granule strength and improved disintegration properties.

EP 277 874 and EP 475 536 describe a technique for coating of cores with a spraying powder containing an active drug and low substituted hydroxypropyl cellulose. As described in EP 361 874 the cores have increased hardness and favourable disintegration properties.

EP 277 127 describes controlled release beads coated with a membrane controlling drug release. The pharmaceutical active compound is dissolved in a solvent and applied onto an insoluble core material with a porosity of less than 15%.

There is not described anywhere in the prior art a controlled release multiple unit system or beads comprising a soluble core, alternatively an insoluble core with a porosity of less than 15% layered with a pharmaceutical practically insoluable

(USP XXIII) active substance dispersed in or homogeneously mixed with a hydrophilic polymer, thereby exhibiting excellent mechanical properties.

Outline of the invention

We have now surprisingly found that the problem mentioned above can be solved by the new pharmaceutical preparation according to the present invention. The invention provides a novel, controlled release multiple unit dose formulation having clinical and pharmaceutical advantages and with excellent compaction characteristics withstanding alteration of the dissolution profiles, and hence no altering of the bioavailability and clinical effect, during the compaction.

When forming the pharmaceutical preparation according to the invention it has surprisingly been found that the addition of a hydrophilic polymer in a layer together with the active substance in specified ratios and the ratio of active substance to the core being within specified ratios in the beads, gives favourable mechanical properties withstanding cracking, especially of the release controlling membrane, when exposed to mechanical stresses, e.g. during filling in capsules or sachets or during compaction.

The active substance is, according to the invention, dispersed in a solution of the hydrophilic polymer and applied to the core. By using powder layering, i.e. simultaneously spraying an aqeous solution of the hydrophilic polymer and the active substance as a drug powder onto the core, the principle according to the invention may be obtained. A solution of the active substance dissolved in a solvent may also be used, whereby the solution of active substance is applied onto the core. A release controlling membrane is further applied to obtain controlled release properties. This membrane may also contain additional polymers i.e. usable as coating materials for pharmaceutical purposes.

The layering technique according to the invention, gives multiple unit systems which exhibit sufficient plasticity and flexibility to withstand cracking or rupturing of the release controlling membrane during compaction, i.e. no significant changes in the release profile characteristics of compressed coated pellets relative to uncompressed coated pellets are seen. A combination of the polymer layering of the core and a controlled release membrane containing polymeric substances as described above is also favourable to improve the compaction properties of the multiple units.

The preparation consists of a large number of small inert and insoluble particles, cores, which are layered with an active compound e.g., furosemid, dispersed in a hydrophilic polymer.

The cores have a size of 0.1 - 2 mm, preferably 0.1 - 0.5 mm, and most preferably 0.1 - 0.3 mm, and consists of insoluble inert material, i.e. not soluble in water or physiological fluids, such as glass particles or sand (silicon dioxide) or a soluable core such as sugar spheres. The core material used according to the invention may also consist of insoluble inert plastic materials, i.e. spherical or nearly spherical core beads made out of polyvinylchloride, polystyrene or any other pharmaceutical acceptable insoluble synthetical polymeric material made into beads or pellets.

The core material should have a standardized size and shape, preferably spherical, it should have a high enough density to make possible fluidizing processes.

The pharmaceutically active compound is applied onto the core material preferably by spraying in a fluidized bed with wurster or top spray technique from a dispersion of the compound in a polymeric solution. To allow the spraying process from a dispersion of the particles the particle size of the active compound have to be small, normally less than 100 mm, more preferably less than 30 mm.

The active compound thereby forms a compact layer together with the polymer on the insoluble core. Resulting particles i.e. the controlled release beads have a size of 0.2 - 3.0 mm, more preferably 0.2 - 1.5 mm, most preferably 0.2 - 0.9 mm when filled into capsules and 0.3 - 1.5 mm for tableting.

The hydrophilic polymer gives the beads plastic properties and even act as a binder. Hydrophilic polymers such as polyvinylpyrrolidone, polyalkylene glycol such as polyethylene glycol, gelatine, polyvinyl alcohol, starch and derivatives thereof, cellulose derivatives such as hydroxymethylpropyl- cellulose, hydroxypropylcellulose, carboxymethyl cellulose, methyl cellulose, propyl cellulose, hydroxyethyl cellulose, carboxyethyl cellulose, carboxymethylhydroxyethyl cellulose or any other pharmaceutically acceptable hydrophilic polymer.

The core particles may be coated with the active substance dispersed in the hydrophilic polymers by powder layering technique, i.e. the active substances is applied to the core in dry form as powder. At the same time the polymer is sprayed onto the cores as a solution in such a way that solvent, preferably water, is evaporated, and the polymer is applied to the cores together with the active substance, i.e. forming a homogenous dispersion.

The ratio of active substance to hydrophilic polymer may be from about 10:1 to about 1:2 for tableting, preferably from about 5:1 to about 1:1, most preferably from about 2:1 to about 1:1, and for filling into capsules preferably from about 10:1 to about 5:1.

The ratio of active substance to inert non-soluble core particles may be from about 5:1 to about 1:2, preferably from about 2:1 to about 1:2.

Preferred active substances are furosemid, carbamazepin, ibuprofen, naproxen, probenecid, indometacin, ketoprofen, spironolactone, felodipin, nifedipin, dipyridamole, pindolol, nitrazepam or dextromethorphan, particularly preferred is furosemid.

The method described above can be used for other pharmaceutical substances as well, provided that they can be dispersed in liquid containing a dissolved hydrophilic polymer, water-based solutions of a hydrophilic polymer is especially preferable. It may even be possible to dissolve the active substance in liquid containing the dissolved polymer prior to spraying onto the cores.

The beads are coated with a polymeric membrane modifying and controlling the drug release. The polymeric membrane can release the drug according to various release profiles, e.g. pH dependent, enteric coating, pH independent, with or without lag time. The most important use is pH independent controlled release in the range of pH 1-8. Examples of suitable polymeric materials are ethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl phtalate (e.g. HP 55), cellulose acetate phtalate, cellulose acetate trimellitate, Eudragit® RL, Eudragit® RS. Ethyl cellulose can be used alone or in a combination with e.g. a water soluble polymer such as hydroxypropylmethyl cellulose to adjust the permeability of the coating layer. Even the copolymerisate of acrylic and methacrylic acid esters or other film-formers mentioned herein may be used in combination with a water-soluble polymer. Other pharmaceutically acceptable polymers which could be incorporated in the film layer are polyvinylpyrrolidone, polyalkylene glycols such as polyethylene glycol, and cellulose derivatives such as hydroxypropyl cellulose, carboxymethyl cellulose, methyl cellulose, propyl cellulose, hydroxyethyl cellulose, carboxyethyl cellulose, carboxymethylhydroxyethyl cellulose, hydroxymethylcellulose, carboxymethylethylcellulose, methyl- hydroxypropylcellulose.

Ethyl cellulose is available in grades having different viscosities. Different kinds of viscosity grades are suitable. Even water-based dispersions of ethylcellulose is suitable.

Eudragit® is the trade name for a number of film coating substances on an acrylic resin basis produced by Röhm Pharma. E.g. Eudragit® RL and RS are copolymers synthetized from acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. The molar ratio of these ammonium groups to the remaining neutral (meth)acrylic acid esters is 1:20 for Eudragit® RL and 1:40 for Eudragit® RS resulting in different permeability characteristics. Other variants of Eudragit® that can be used are Eudragit® L, Eudragit® S and Eudragit® E.

Pigments and/or plasticizers may be added to the polymeric solution in order to improve the technical properties of the membrane or modify the release characteristics. Examples of plasticizers that may be used are citrate esters, acetylated monoglycerides, and glycerinetriacetate.

Organic solutions or water-based dispersions of the polymers, as will be appreciated by the man skilled in the art (e.g Aquacoat®, Surelease®, Eudragit® E 30 D, Eudragit® L 30 D) could be used for obtaining the membrane modifying and controlling the release of the active substance.

By using the pharmaceutical preparation according to the invention several advantages are obtained.

The coated beads or multiple units described above are favourable in obtaining coated beads filled into capsules or sachets. Especially advantageous according to the invention is when the beads are compressed into tablets. By using the pharmaceutical preparation according to the invention it is possible to compress coated beads into tablets without altering the dissolution profile as a consequence of the mechanical

stress during the compaction process. A combination of the layering method described herein and the controlled release film formulation described herein, comprising the film former and a polymeric substance is especially favourable to obtain the excellent compaction characteristics without altering the dissolution profiles, and hence the bioavailability and clinical effect, during compaction.

Use of organic solvents give rise to enviromental pollution, danger of explosions and hazard unless costly recycling procedures are used. From an enviromental point of view the invention is especially favourable as it is possible to layer core material with active substances such as furosemid etc., or other water insoluble substances, by using a dispersion of the active compound in an aqeous solution of hydrophilic polymer, thus without using a solution in organic liquids.

By using powder layering, i.e. simultaneously spraying of an aqueous solution of the hydrophilic polymer and the active substance as dry powder onto the core material, similar enviromental advantages are obtained.

A further advantage with the formulation according to the invention is the incorporation of a hydrophilic polymer together with the active pharmaceutical agent. This may give more favourable possibilities to control the dissolution profile of the uncoated and coated beads, for furosemid at pH values lower than about 4.

The preparation according to the invention is particularly advantageous when controlled and constant release of the therapeutical agent is wanted. A method for the controlled release of the therapeutically active substance e.g., furosemid is a further aspect of the invention. Thus giving flexibility and favourable mechanical properties in such a way that cracking or rupturing of the release controlling membrane is avoided.

Pharmaceutical preparations

The formulation above comprising multiple unit dose systems with a release controlling membrane may be prepared by conventional methods such as fluidized beds with top-spray or wurster techniques or powder layering techniques, or any technique well known to one skilled in the art.

When the pellets are compressed into tablets they are blended with conventional excipents to obtain favourable filling, binding, lubrication and disintegration properties. Examples of excipients are microcrystalline cellulose, lactose, spray dried lactose, dicalcium phosphate, pregelatinized starch, starches and derivatives thereof such as sodium starch glycolate, maltodextrine, sorbitol, maltitol, cellulose and derivatives thereof, polyethylene glycol, polyvinyl pyrrolidone, compressable sugar, stearic acid, magnesiumstearat, sodium stearylfumarate, talc, colloidal silicone dioxide or any other conventional excipient usable for tablet preparation as will be clear to anyone skilled in the art.

The excipients, i.e. the fillers and binders, comprising the tablet may be used as direct compression excipients or they may be granulated into granules with favourable compression characteristics. Disintegrats may or may not be added. Lubricants will normally be added. The amount of fillers and binders, eventually granulated into granules, may be in the range from 25 to 75% of the total tablet weight. To obtain even more favourable compression characteristics it should be between 40 and 75% of the total tablet weight.

The pharmaceutical preparations according to the present invention may be administered orally. Substances, such as furosemid, which are excellent as a medicament against cardiovascular diseases such as hypertension, congestive heart failure and oedema, especially for the treatment of hypertension are of special interest.

Other active substances could be used, e.g. substances for the treatment of diuretic, antiepileptic, antiinflammatoric, analgetic conditions.

The following examples will describe the invention in more detail.

Example 1

Cores:	
Silicone dioxide (0.1-0.3 mm)	1000 g
Water, purified	2000 g
Furosemid (90%<25µm)	1000 g
Polyvinyl pyrrolidone, K-30	500 g
Polymeric Layer:	
Ethylcellulose	60.3 g
Hydroxypropylmethylcellulose	13.3 g
Triethylcitrate	6.0 g
Ethanol	1446.5 g

Examples 2-4

Cores:	
Silicone dioxide (0.1-0.3 mm)	800 g
Water, purified	1480 g
Furosemid (90%<10µm)	800 g
Polyvinyl pyrrolidone, K-30	400 g

Polymeric layers:

	Example 2	
	Ethylcellulose	292 g
5	Hydroxypropylcellulose	108 g
	Ethanol	3500 g
	Example 3	
	Ethylcellulose	266 g
10	Hydroxypropylcellulose	134 g
	Ethanol	3500 g
	Example 4	
	Etylcellulose	240 g
15	Hydroxypropylcellulose	160 g
	Ethanol	3500 g

In a fluidized bed granulator furosemid dispersed in a solution of polyvinyl pyrrolidone (K-30) in water was sprayed onto the cores of silicone dioxide. 800 g of the beads so
20 formed were covered with the polymeric solution containing ethyl cellulose and hydroxypropylmethylcellulose, and triethylcitrate in Example 1, ethyl cellulose and hydroxypropylcellulose in Example 2-4, by spraying a solution of the mentioned substances in ethanol.

25 Formulation examples 5-7

The pellets formed according to Example 1 were compressed into tablets containing furosemid in an amount of 30-60 mg. The small beads were thus tabletted by mixing with additives containing e.g. microcrystalline cellulose such as Avicel ®, which

improves the tableting properites and facilitates the disintegration of the tablet to liberate the individual beads.

Composition for one tablet (mg)

Example 5	
Coated pellets (Example 1)	171.8
Microcrystalline cellulose (Avicel® PH 200)	171.8
Sodium starch glycolate	13.7
Magnesium stearate	0.4
Example 6	
Coated pellets (Example 1)	171.8
Microcrystalline cellulose (Avicel® PH 102)	171.8
Sodium stearylfumarate	0.3
Example 7	
Coated pellets (Example 1)	171.8
Microcrystalline cellulose (Avicel® PH 102)	171.8
Sodium starch glycolate	13.7
Sodium stearylfumarate	0.3

The multiple unit pellets described in Example 1 were mixed with equal amounts of microcrystalline cellulose, and further mixed with 4% sodium starch glycolate (example 5 and example 7). Magnesium stearate (example 5) or sodium stearylfumarate (example 6 and example 7) was admixed, and the mixtures were compressed into tablets in a singel punch tablet press at a compression pressure of 8 kN (± 1 kN) and 4 kN (± 1 kN) at a compression speed of 35 rpm. Flat faced punch with a diameter of 1.13 cm was used.

Characterization of the tablets according to example 5

The tablets disintegrated into multiple unit pellets within 30 seconds in 1000 ml purified water at 37°C.

The in vitro dissolution, in accordance with USP Paddle method, 1000 ml buffer pH 6.8, of the tablets compressed at 8 kN, containing 60 mg furosemid, is shown in Table 1.

Reference 1

Cores:	
Silicone dioxide (0.15-0.25 mm)	1000 g
Water, purified	1950 g
Furosemid (90%<25 µm)	1000 g
Polyvinyl pyrrolidone, K-90	50 g

Polymeric Layer:	Ref. 1
Ethylcellulose dispersion, 30% (Aquacoat®)	170 g
Acetyltributyl citrate	13 g

In a fluidized bed granulator furosemid dispersed in a solution of polyvinyl pyrrolidone (K-90) in water was sprayed onto the cores of silicone dioxide. 800 g of the beads so formed were coated with the aqueous polymeric ethylcellulose dispersion, (Aquacoat®) containing additional plasticizer acetyltributyl citrate. After the coating procedure the coated pellets were heated for 17 hours at 70°C.

The beads described were further, as described in example 5, mixed with equal amounts of microcrystalline cellulose, and further mixed with 4% sodium starch glycolate and 0.1% magnesium stearate and compressed into tablets in a singel punch tablet press at a compression pressure of 8 kN (± 1kN) at a compression speed of 35 rpm. Flat faced punch with a diameter of 1.13 cm was used. The tablets contained 60 mg furosemid.

Table 1 illustrates the release pattern in vitro for ethylcellulose coated beads.

Table 1

Dissolution of furosemid from furosemid tablets, 60 mg, prepared according to example 5 and reference 1.

	Percentage furosemid released at pH 6.8 (n=3) after:					
	0.5h	1h	2h	3h	5h	10h
Example 5	18%	33%	52%	65%	79%	>90%
Reference 1	41%	60%	>80%			

(n=2)

As is shown in table 1 the pellets when compressed into tablets according to example 5, showed sustained or extended release properties even when compressed into tablets, whereas pellets prepared according to reference 1 released furosemid relatively fast. The amount of ethylcellulose and plasticizer in relation to pellets was 8% by weight in example 5 and reference 1.

Example 8

The pellets formed according to Example 1 were filled into hard gelatine capsules.

Example 9 and 10

Cores:

Silicone dioxide (0.1-0.3 mm)	1000 g
Water, purified	1900 g
Furosemid (90%<25 µm)	1000 g
Polyvinyl pyrrolidone, K-90	100 g

Polymeric Layer:

Example 9

Ethylcellulose dispersion, 30% (Aquacoat)	128 g
Acetyltributyl citrate	10 g

Example 10

Ethylcellulose dispersion, 30% (Aquacoat)	170 g
Acetyltributyl citrate	13 g

In a fluidized bed granulator furosemid dispersed in a solution of polyvinyl pyrrolidone (K-90) in water was sprayed onto the cores of silicone dioxide. 800 g of the beads so formed were coated with the aqueous polymeric ethylcellulose dispersion, (Aquacoat) containing additional plastizer acetyltributyl citrate. After the coating procedure the coated pellets were heated for 17 hours at 70°C.

The pellets were finally filled into hard gelatine capsules. Each capsule contained 60 mg furosemid.

The in vitro dissolution of the capsules in accordance with USP Paddle method, 1000 ml buffer pH 6.8, is shown in Table 2.

Table 2

Dissolution of furosemid from furosemid capsules, 60 mg, prepared according to examples 9 and 10.

	Percentage furosemid released at pH 6.8 (n=6) after:						
	0.5h	1h	2h	3h	5h	10h	13.3h
Example 9	31%	48%	67%	75%	>90%	-	-
Example 10	10%	19%	33%	44%	60%	70%	>80%

Formulation Examples 11-24

The pellets formed according to the above given examples 2-4 were compressed into tablets containing furosemid in an amount of 60 mg.

Compositions for one tablet (mg)

	Example 11	
	Coated pellets (example 2)	221
	Microcrystalline cellulose (Avicel sp. coarse grade)	331
5	Sodium starch glycolate	22
	Magnesium stearate	0.28
	Example 12	
	Coated pellets (example 2)	221
10	Microcrystalline cellulose (Avicel PH 302)	331
	Sodium starch glycolate	22
	Magnesium stearate	0.28
	Example 13	
15	Coated pellets (example 2)	221
	Microcrystalline cellulose (Avicel sp. coarse grade)	331
	Sodium stearylfumarate	0.20
	Example 14	
20	Coated pellets (example 2)	221
	Microcrystalline cellulose (Avicel sp. coarse grade)	331
	Crospovidone	22
	Sodium stearylfumarate	0.20

25 The multiple unit pellets described in example 2 were mixed with 60 % microcrystalline cellulose, and further mixed with 4 % sodium starch glycolate (example 11 and 12) or Crospovidone (example 14). Magnesium stearate (example 11 and 12) or sodium stearylfumarate (examples 13 and 14) was admixed and, the mixtures were compressed into tablets in a single punch tablet press at a compression

pressure of 8 kN (+/- 0.4 kN) at a compression speed of 30 rpm. Flat faced punches with a diameter of 1.13 cm were used.

	Example 15	
	Coated pellets (example 3)	221 mg
	Microcrystalline cellulose (Avicel sp.coarse grade)	221 mg
	Sodium starch glycolate	18 mg
	Magnesium stearate	0.22 mg
	Example 16	
	Coated pellets (example 3)	221 mg
	Microcrystalline cellulose (Avicel PH 302)	221 mg
	Sodium starch glycolate	18 mg
	Magnesium stearate	0.22 mg
	Example 17	
	Coated pellets (example 3)	221 mg
	Microcrystalline cellulose (Avicel sp. coarse grade)	331 mg
	Magnesium stearate	0.28 mg
	Sodium starch glycolate	22 mg
	Example 18	
	Coated pellets (example 3)	221 mg
	Microcrystalline cellulose (Avicel sp.coarse grade)	221 mg
	Sodium stearylfumarate	0.18 mg

Example 19

Coated pellets (example 3)	221 mg
Microcrystalline cellulose (Avicel sp. coarse grade)	221 mg
Crospovidone	18 mg
Sodium stearylfumarate	0.18 mg

The multiple unit pellets described in example 3 were mixed with 50 or 60 % microcrystalline cellulose, and further mixed with 4 % sodium starch glycolate (example 15-17) or Crospovidone (example 19). Magnesium stearate (example 15-17) or sodium stearylfumarate (example 18 and 19) was admixed and, the mixtures were compressed into tablets in a single punch tablet press at a compression pressure of 12 kN (+/- 0.6 kN) and 16 kN (+/- 0.8 kN) at a compression speed of 30 rpm. Flat faced punches with a diameter of 1.13 cm were used.

Example 20

Coated pellets (example 4)	223 mg
Microcrystalline cellulose (Avicel sp.coarse grade)	334 mg
Sodium starch glycolate	22 mg
Magnesium stearate	0.28 mg

Example 21

Coated pellets (example 4)	223 mg
Microcrystalline cellulose (Avicel PH 302)	334 mg
Sodium starch glycolate	22 mg
Magnesium stearate	0.28 mg

Example 22	
Coated pellets (example 4)	223 mg
Microcrystalline cellulose (Avicel sp.coarse grade)	334 mg
Sodium stearylfumarate	0.20 mg

Example 23	
Coated pellets (example 4)	223 mg
Microcrystalline cellulose (Avicel sp. coarse grade)	334 mg
Crospovidone	22 mg
Sodium stearylfumarate	0.28 mg

The multiple unit pellets described in example 4 were mixed with 60 % microcrystalline cellulose, and further mixed with 4 % sodium starch glycolate (example 20 and 21) or Crospovidone (example 23). Magnesium stearate (example 20 and 21) or sodium stearylfumarate (example 22 and 23) was admixed, and the mixtures were compressed into tablets in a single punch tablet press at a compression pressure of 8 kN (+/- 0.4 kN) and 16 kN (+/- 0.8 kN) at a compression speed of 30 rpm. Flat faced punches with a diameter of 1.13 cm were used.

Characterization of the tablets formed according to formulation examples 11-21

The tablets disintergrated into multiple unit pellets within 3 minutes in 1000 ml purified water at 37° C.

The in vitro dissolution, in accordance with USP Paddle method, 1000 ml buffer pH 6.8, of the tablets compressed at 8, 12 and 16 kN, containing 60 mg furosemid, is shown in Table 3.

Table 3

Percentage furosemide at pH 6.8 (n=3)

Examples	Compaction Pressure (kN)	Percent furosemide dissolved at pH 6.8 (min)							
		30	60	120	180	300	600	840	1200
2	-	1	2	4	8	19	56	80	96
11	8	1	2	5	10	24	69	91	100
12	8	1	2	5	9	23	67	90	98.4
3	-	13	22	56	88	100			
15	12	12	21	50	82	100			
16	12	9	18	46	79	100			
17	16	8	17	49	84	100			
4	-	14	34	83	100				
20	8	11	36	90	100				
20	16	12	39	97	100				
21	8	11	38	98	100				

Example 24

Core:

Silicone dioxide (0.1-0.3 mm)	800 g
Water, purified	1480 g
Naproxen	800 g
Polyvinyl pyrrolidone, k-30	400 g

Polymeric layer:

Ethylcellulose	266 g
Hydroxypropylcellulose	134 g
Ethanol	3500 g

Composition of one tablet (mg)

Coated pellets (example 24)	247
Microcrystalline cellulose (Avicel sp. coarse grade)	370
Sodium starch glycolate	25
Magnesium stearate	0.31

The multiple unit pellets described in example 24 were mixed with 60 % microscrystalline cellulose, and further mixed with 4 % sodium starch glycolate. Magnesium stearate was admixed and, the mixture was compressed into tablets in a single punch tablet press at a compression pressure of 8 kN (+/- 0.4 kN) at a compression speed of 30 rpm. Flat faced punches with a diameter of 1.13 cm were used.

The in vitro dissolution, in accordance with USP paddle method, 1000 ml buffer pH 7.4, of the tablets compressed at 8 kN, containing 60 mg Naproxen, is shown in Table 4.

Table 4

Percentage naproxen at pH 7.4 (n=3)

Exampel 24	Compaction Pressure	Percent naproxen dissolved at pH 7.4 30	60	120	180	300
Pellets	-	10	30	76	96	99
Tablets	8	9	32	79	98	100

Conclusion

By using the principles described herein reproducible and controllable production processes for multiple unit systems compressed into tablets or filled into capsules or sachets are obtained. Further this new formulation principle gives excellent multiple unit systems withstanding mechanical stresses and giving enough flexibility and plasticity to avoid cracking or rupturing of release controlling membranes.

CLAIMS

1. Controlled release beads with a size of 0.2 - 3.0 mm, comprising cores of an insoluble or soluable inert material with a size of 0.1 - 2 mm, optionally layered with a first inner layer of hydrophilic polymer, said core or said core optionally layered with the first inner layer of hydrophilic polymer being layered with active substance dispersed in a hydrophilic polymer, the ratio of active substance to hydrophilic polymer being in the range of from about 10:1 to about 1:2 and the ratio of active substance to inert insoluble or soluable core being in the range of from about 5:1 to about 1:2, said active substance being optionally layered with an outer layer of hydrophilic polymer, and with an outer membrane for controlled release of the active substance, wherein the beads have excellent mechanical characteristics and release properties.

2. Controlled release beads according to claim 1 wherein the ratio of active substance to hydrophilic polymer being in the range of from about 2:1 to about 1:2.

3. Controlled release beads according to claim 1, wherein the cores have a size of 0.1 - 0.3 mm.

4. Controlled release beads according to claim 3, wherein the core is layered with the active substance dispersed in a hydrophilic polymer, which in turn is layered with an outer membrane for controlled release.

5. Controlled release beads according to claim 4, wherein the hydrophilic polymer is polyvinyl pyrrolidone.

6. Controlled release beads according to claim 1, wherein the beads have a size of 0.2-1.5 mm.

7. Controlled release beads according to claim 4, wherein the active substance is furosemid.

8. A process for the preparation of controlled release beads according to claim 1, wherein the pharmaceutical active compound is an active substance having a particle size of less than 100 µm is dispersed in a solution of a hydrophilic polymer, sprayed onto the insoluble inert cores, or said cores optionally layered with a first inner layer of hydrophilic polymer, giving a layer of active substance and thereafter the outer membrane for controlled release is sprayed onto the previous layer, optionally an outer layer of hydrophilic polymer can be sprayed on before the controlled release layer.

9. A process according to claim 8, wherein the hydrophilic polymer is polyvinyl pyrrolidone.

10. A pharmaceutical preparation comprising controlled release beads according to claim 1, optionally together with pharmaceutically acceptable excipients.

11. A pharmaceutical preparation according to claim 10, wherein the active substance is furosemid.

12. A pharmaceutical preparation according to any one of claims 10 or 11, wherein the amount of active substance is in the range 20 - 100 mg.

13. A pharmaceutical preparation according to claim 12, wherein the amount of active substance is in the range 30 - 60 mg.

14. A pharmaceutical preparation according to any one of claims 12 or 13, in the form of tablets, having excellent compaction characteristics.

15. A pharmaceutical preparation according to claim 14, wherein the ratio of active substances to hydrophilic polymer is of from about 5:1 to about 1:1 and the ratio of active substance to inert non-soluble core particles is of from about 2:1 to about 1:2.

16. A pharmaceutical preparation according to claim 15, wherein the ratio of active substance to hydrophilic polymer is of from about 2:1 to about 1:1 and the ratio of active substance to inert non-soluble core particles is of from about 2:1 to about 1:2.

17. A pharmaceutical preparation according to claim 12, in the form of capsules.

18. A pharmaceutical preparation according to claim 17, wherein the ratio of active substance to hydrophilic polymer is of from about 10:1 to about 5:1 and the ratio of active substance to inert non-soluble core particles is of from about 2:1 to about 1:2.

19. A pharmaceutical preparation according to claims 10-18 which is administered orally.

20. A process for the manufacture of a pharmaceutical preparation according to claim 14, wherein the cores are compressed into tablets by mixing with additives.

21. Use of controlled release beads according to claim 1 in the manufacture of a medicament for the treatment of cardiovascular diseases such as hypertension, congestive heart failure and oedema.

22. A method for the treatment of hypertension, oedemas and congestive heart failure wherein a pharmaceutical preparation according to claim 10-19 is administered to a host in the need of such treatment.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/00676

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/16, A61K 9/26, A61K 9/54, A61K 31/34
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK;FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EMBASE, MEDLINE, WPI, WPIL, CLAIMS, CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0475536 A1 (TAKEDA CHEMICAL INDUSTRIES, LTD), 18 March 1992 (18.03.92) --	1-21
X	WO 8503436 A1 (A/S ALFRED BENZON), 15 August 1985 (15.08.85) --	1-21
A	EP 0452862 A2 (ASAHI KASEI KOGYO KABUSHIKI KAISHA), 23 October 1991 (23.10.91) --	1-21
A	EP 0305918 A1 (AIR PRODUCTS AND CHEMICALS, INC.), 8 March 1989 (08.03.89) -- --------	1-21

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 October 1995	21 -10- 1995
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/00676

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 22
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/SE 95/00676

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		DE-D- 69111287	00/00/00
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		DE-A- 3876724	28/01/93
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